NAFTA Regulatory Actions – Completed in 2002

- ✓ **Registration of mixture products**
  - Camix & Lumax July 29,
  - Dow product July 5
- ✓ **Petition for expanded use to Sweet Corn**
  - Reduced Risk status – April 2002
  - Include rebuttals to aspects of June 2001 registration
  - Include expanded use to Pop Corn (through IR4)
- ✓ **Submit Canadian AI Registration Package**

US CONDITIONS OF REGISTRATION (1)

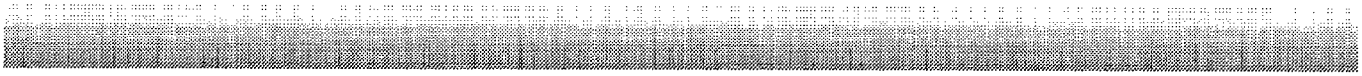
- US Conditions of registration clarified by EPA in Lumax conditional registration notice
- Syngenta has mainly rebutted, with some work in progress

Ongoing work:

- Non-target plant program – redo with adjuvant
  - 123-1 (a) and (b) – Tier II Seed Germination/Seedling Emergence & Tier II Vegitative Vigor
  - 123-2 – Tier II Aquatic Plant Growth

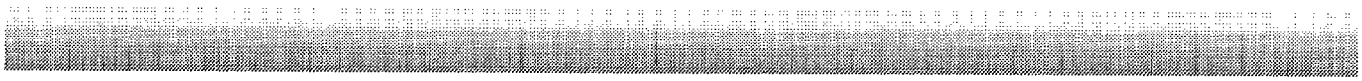
US CONDITIONS OF REGISTRATION (2)

- **Rebuttals to other conditions w/sweet corn petition**
  - **Medium to high probability of success:**
    - **860-1340 (confirmatory method in lieu of revised interference study)**
    - **870-3465 (28-day inhalation)**
    - **860-1300 (plant and livestock metabolism storage stability)**
    - **164-1 soil extraction procedure**
  - **Lower probability of success:**
    - **166-1 (PGM) – to be clarified by mid-October**
    - **870-3465 (DNT) – preliminary work started (?)**



NAFTA Regulatory ongoing activities

- Carryover
- Manufacturing
  - New Specification
    - Registration of scale-up vs. pilot process
  - Increase Capacity
  - Ames



Ames (1)

- History
  - Early in mesotrione development, a batch produced in the lab was high ames
  - Isolated to XAN1, which was removed through removal of precursers in starting material NMSBA
  - Further testing showed very low ames responses
  - Attempts to isolate other trace nitroxanthenones have been met with some success
  - Identification of all nitroxanthenones responsible for the small ames responses difficult
    - Assat limitations: At or below lower limit of ames bioassay (1.8 – 2.5)
    - Complexity: Trace levels and multitude of compounds

Ames (2)

- Various groups have tried to "solve" this issue (prod chem, manufacturing, regulatory) → no quick fix
- Latest initiative = small team: Kambiz Javdani (CC), Madan Verma (prod tech), Barry Elliott (AP), Dan Campbell (US reg), Fredi Seiler (GRA), Charlotte Croudace (EU reg).
  - Proposals made for US EPA submission as part of scale-up manufacturing specification, with generation of more data.
    - Requires that EPA accepts ames ~2.8 not toxicologically significant
    - Requires "freezing" of manufacturing process
    - 5-typical batch
    - More direct validation of NMSBA impurity leads to ames +
    - Validation of chemical method to replace ames bioassay
    - Investigation of variability in ames and implications to bioassay results.

Ames (3)

- Proposal made to Devco 9/9, and not accepted
  - Quick fix vs. Severe risks to business
- Business wants flexibility during further scale-up

⇒Continue ames bioassay for trace active impurities for now

⇒Continue to develop data for potential EPA submission

⇒Continue with current team

HCN

- Successfully evaluated for Callisto
  - Concentration in AI, product, headspace, worker inhalation, and tank mix
  - Need closure from toxicology that current spec is acceptable
  - No regulatory submission
- Need same evaluation for Lumax and Camix bulk scenarios